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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,226	01/20/2004	Philip C. Gevas	1102865-0031 CON	2197
7470	7590	11/01/2005	EXAMINER	
WHITE & CASE LLP PATENT DEPARTMENT 1155 AVENUE OF THE AMERICAS NEW YORK, NY 10036			UNGAR, SUSAN NMN	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/762,226

Applicant(s)

GEVAS ET AL.

Examiner

Susan Ungar

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 25 August 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/17/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

1. The Amendment filed August 25, 2005 in response to the Office Action of March 23, 2005 is acknowledged and has been entered. Claims 1-5 currently being examined.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. Claims 2 remains rejected under 35 USC 112, second paragraph for the reasons previously set forth in the action mailed March 23, 2005, page 2.

Applicant argues that one of ordinary skill would readily understand that the “immunogen” of claim 2 relates to the immunogenic composition of claim 1 and since there is no requirement that there be an *ipsis verbis* correspondence between the claim terms and their support, in this case the antecedent basis in claim 1, the rejection should be withdrawn. The argument has been considered but has not been found persuasive because although it is apparent that the term immunogen of claim 2 relates to the immunogenic composition of claim 1, since claim 1 is drawn to an immunogenic composition it cannot be determined from claim 1 whether there are one or more immunogens in that composition and it cannot be determined which “immunogen” is referred to in claim 2. It is suggested that Applicant review MPEP 2173.05(e) for further information. The arguments have been considered but have not been found persuasive and the rejection is maintained. Amendment of claim 2, for example, to delete the term ‘immunogen’ and substitute therefore the phrase “immunogenic composition” would obviate the instant rejection.

New Grounds of Objection

Specification

4. The specification on page 1 should be amended reflect the priority claims to parent applications.

New Grounds of Rejection

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the claimed invention.

The claims are drawn to a method for the treatment of glycine-extended gastrin-17-dependent gastrointestinal tumors, comprising administering to a mammal a therapeutically effective amount of an anti-G-17 immunogenic composition.

The specification teaches that the immunogen used in the exemplification of the claimed inventions binds to both amidated and glycine-extended G17 but not to G34 (p. 11) and that anti-G17 immunization resulted in the potential neutralization of two trophic forms of gastrin, G17 and glycine-extended G17. Cytostasis within the tumors was induced. The histological observations of colorectal cell line DHDK12 tumors provides evidence, that in this model, treatment with anti-G17

immunogen slowed growth rate of the tumor in rat and reduced viable tumor area compared to untreated controls (p. 23).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification has not identified a single glycine-extended G17 dependent tumor and has not taught how to identify glycine-extended G17 dependent tumors. In particular, dependence of a tumor on a particular protein suggests that the protein is at least necessary for the initiation, progression or maintenance of the tumor. The dependence of any gastrointestinal tumor on glycine-extended gastrin-17 has not been established either in the specification or the art of record and the role of glycine-extended gastrin-17 in carcinogenesis is the subject of controversy and speculation. In particular, as drawn to the specification, it is noted that the method disclosed in Example 6 specifically resulted in the "potential neutralization of two trophic forms of gastrin". The dependence of the tumors on the glycine extended form of gastrin was not established. The specification does not teach how to distinguish between the anti-amidated and glycine-extended G17 effects of the immunogen. Further, as drawn to literature, Watson et al (Cancer Res., 1996, 56:880-885, of record), published 8 days after the filing of parent US application serial number 60/011,411, teach that gastrin is a well-recognized growth factor for human colorectal adenocarcinomas and that the 17 amino acid form, G17 appears to be particularly implicated in this effect and that an autocrine growth loop, possibly involving gastrin precursors has been postulated to be involved in the proliferation of gastrointestinal tumors and teach that the observations of a mitogenic potency of glycine-extended gastrin-17 raises the question of a possible autocrine role of processing intermediates of gastrin, which needs to be examined. Although the instant specification again

raises the question of the role of the glycine extended precursor, it provides no information drawn to the dependence of any tumor on the glycine extended precursor and does not teach how to identify the glycine-extended precursor-dependent tumor. Further, Rehfeld (Gastroenterology, 1995, 108(4)1307-1310) teaches that glycine-extended gastrins have not been shown to have significant growth-promoting effects on gastric mucosal cells. It has been speculated that perhaps glycine-extended gastrins stimulate growth of other cells. The speculation was nurtured by direct demonstration of a growth-promoting effect of glycine-extended gastrins on a rat pancreatic cell line. The question about possible effects of gastrin on colorectal cancers requires consideration of glycine-extended gastrins. Although conceptually controversial, the idea of glycine-extended processing intermediates as growth factors has to be taken into account (p. 1308, col 1). Further, Ciccotosto et al (Gastroenterology, 1995, 109(4)1142-1153, IDS item) teaches that the majority of colorectal cancers produce gastrin and show an increase in nonamidated gastrin levels in the circulation. Whether this hypergastrinemia is of pathological importance or whether the gastrin contained in the tumor functions as an autocrine growth factor remains to be determined (p. 1151, para 4). Given the above, it is clear that specification is deficient in the identification of the glycine-extended gastrin 17-dependent tumors because it does not appear that it was in fact known in the art, at the time the invention was made, that there were in fact glycine-extended gastrin 17-dependent tumors or which tumors were glycine-extended gastrin 17-dependent tumors and the specification does not teach which gastrointestinal tumors are glycine-extended gastrin 17-dependent tumors, a teaching clearly required by the claims.

Further, the claims as currently constituted are drawn to active immunization (vaccination) against glycine-extended G17 in humans for the treatment of cancer. However, the specification provides no exemplification of or guidance on how to use the claimed method comprising an immunogenic composition for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49, IDS item) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single immunogen will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3, IDS item) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210, IDS item) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). There is

no suggestion in the specification or in the art that the expression of glycine extended Gly-17 has resulted in autoantibodies against the antigen thus it would be highly unpredictable that administration of the antigen as a cancer vaccine, into patients that already express a heavy load of the antigen in serum, would lead to an immune response against the tumor.

In view of the contemporary knowledge in the art of the general lack of successful application of cancer vaccines for the treatment of human diseases as discussed above as well as the unpredictability in the art pertaining to the immune response in patients with large tumor burdens as discussed above as well as the lack of sufficient guidance in the specification drawn to any glycine-extended gastrin-17 dependent gastrointestinal tumors, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

7. Claims 1-5 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-5 are drawn to a method of treatment of glycine-extended gastrin-17 dependent gastrointestinal tumors. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that “[a] written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to

distinguish it from other materials.” *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA” without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. “A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” *Id.*

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description requirement can be met by ‘show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional

characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. ” Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a glycine-extended gastrin-17 dependent gastrointestinal tumor itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of glycine-extended gastrin-17 dependent gastrointestinal tumor, per Lilly by structurally describing a representative number of glycine-extended gastrin-17 dependent gastrointestinal tumor or by describing “structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Alternatively, per Enzo, the specification can show that the claimed invention is complete “by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.”

In this case, the specification does not describe glycine-extended gastrin-17 dependent gastrointestinal tumor required to practice the method of claim 1 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any glycine-extended gastrin-17 dependent gastrointestinal tumor, does not describe any structure on said tumors that might be associated with said dependence, nor does the specification provide any partial structure of, nor any physical or chemical characteristics of the glycine-extended

gastrin-17 dependent gastrointestinal tumor nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single murine model of a DHDK12 rat colon cell line derived tumor, the specification does not distinguish between antibody effects against amidated gastrin and glycine extended gastrin and it is not possible to determine from the information in the specification or the art of record whether the DHDK12 rat colon cell line is in fact a glycine-extended gastrin-17 dependent gastrointestinal tumor and this does not provide a description of glycine-extended gastrin-17 dependent gastrointestinal tumor that would satisfy the standard set out in Enzo.

The specification also fails to describe the glycine-extended gastrin-17 dependent gastrointestinal tumor by the test set out in Lilly. The specification describes does not describe a single glycine-extended gastrin-17 dependent gastrointestinal tumor, therefore, it necessarily fails to describe a “representative number” of such species. In addition, the specification also does not describe “structural features common to the members of the genus, which features constitute a substantial portion of the genus.”

Thus, the specification does not provide an adequate written description of the glycine-extended gastrin-17 dependent gastrointestinal tumor that is required to practice the claimed invention. Since the specification fails to adequately describe the product to be treated, it also fails to adequately describe the claimed method.

8. Claims 1-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

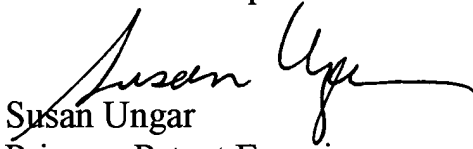
Claims 1-5 are indefinite because claim 1 recites "a method for the treatment of glycine-extended gastrin-17-dependent gastrointestinal tumors". The claim is confusing because it is not clear what is meant by the term "dependent", for example, are the tumors dependent upon glycine extended G17 for initiation, progression or maintenance of the tumor, or is G17 necessary but not sufficient or necessary and sufficient for the recited processes?

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.


Susan Ungar
Primary Patent Examiner
October 28, 2005